Double Patenting

The Examiner rejected claims 3 and 5 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of U.S. Patent No. 5,843,726 (hereinafter the '726 patent). A double-patenting rejection cannot be asserted against claims 3 and 5 of the present invention because those claims and claim 4 of the '726 patent were subject to a restriction requirement.

Application Serial No. 08/106,815, filed August 16, 1993, as originally filed contained claims 1-7. A restriction requirement was made and Group I: claims 1, 2 and 7 were initially elected and prosecuted. Group I claims have subsequently issued on 1 December 1998 as U.S. Patent No. 5,843,726 with claim 7 renumbered as claim 4. Divisional Application Serial No. 08/460,525, was filed June 2, 1995. A second restriction requirement was made and claims 3 and 5 were elected and are now pending in the current application. 35 U.S.C. § 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made as a reference against any divisional application. Therefore, double patenting is nullified as a ground for rejection. MPEP § 804.01.

Claims 3 and 5 have been amended to more clearly direct the invention to the erythropoietin receptor extracellular domain peptide that was the subject matter of that group under the restriction requirement. The claims as amended are patentably distinct from claim 4 of U.S. Patent No. 5,843,726, which is directed to a purified fusion protein. Applicant requests that the double-patenting rejection of claims 3 and 5 over claim 4 of the '726 patent be withdrawn.

35 U.S.C. § 102b

Claims 3 and5 were rejected under 35 U.S.C. § 102(b) as being anticipated by Harris et al. (JBC 1992)[hereinafter referred to as "Harris"].

Claim 3, as amended, is drawn to the extracellular domain of human EPO receptor after it is cleaved from the fusion protein and purified. The inventive extracellular domain of

human EPO receptor is described within the Specification as EPO-bp. Harris does not produce a purified erythropoietin receptor extracellular domain peptide. Harris produces a fusion protein attached to the amino terminal portion of the EPO receptor. Both Harris and the present invention take advantage of the GST moiety to purify a fusion protein using Glutathione (GSH) coupled to a solid support. The present invention takes further steps to cleave the EPO-bp from the fusion protein and purifies the peptide using an EPO affinity column.

Harris purifies the fusion protein but is not successful in cleaving and separating the extracellular domain from the fusion protein. In additional support of this point; a declaration by the inventor of the present application, which was previously submitted in the related prosecution of application 08/850,293 resulting in U.S. Patent No. 5,843,726. The present application is a divisional of parent U.S. Application Serial No. 08/106,815, filed August 16, 1993 resulting in the '726 patent. The declaration presents evidence that the fusion protein of Harris is not cleaved.

In reference to the amended claim 5, the extracellular domain EPO-R peptide of the present invention, named in the specification as EPO-bp, is bound to a solid phase support, namely beads. Contrast to Harris, where it is the fusion protein which is attached to glutathione (GSH) agarose beads. The fusion protein is intact (not cleaved) and includes the GST domain because it is through high affinity interaction between the GST domain and glutathione (GSH) that the fusion protein is operably coupled to the bead. This is a different structural entity from that of amended claim 5.

In summary, amended claims 3 and 5 are not anticipated by Harris et al. (JBC 1992).

35 USC §102a

The examiner rejected claims 4, 6, 10 under 35 U.S.C. § 102(a) as being anticipated by Elliot et al.(JBC 1996) [hereinafter referred to as "Elliot"]. Elliot is improperly asserted as a prior art reference. The priority date for this application is August 16, 1993 as noted

by the continuation information above, predating the publication of Elliot. The Examiner is respectfully requested to withdraw the rejection of claims 4, 6, and 10 as anticipated by Elliot.

35 USC §103

The Examiner rejected claims 4, 6, 8, 9, and 10 under 35 U.S.C. § 103 as being obvious over Harris in view of D'Andrea et al. U.S. Patent No. 5,378,808 [hereinafter referred to as "D'Andrea"]. The Examiner asserted that the teachings of Harris for antibody production to a fusion protein in combination with the truncated proteins of D'Andrea renders the present invention obvious.

D'Andrea in combination with Harris does not teach the invention of claims 4, 6, 8, 9, and 10. Claims 4 and 8 are directed to a purified antibody produced against EPO-bp. Claims 6 and 9 incorporate that antibody into an immunoassay composition. Claim 10 is directed to a method for obtaining an antibody to EPO-bp. Neither Harris nor D'Andrea teach the extracellular domain peptide, EPO-bp, of the present invention and consequently cannot teach the production of antibodies from EPO-bp. Additionally, neither Harris nor D'Andrea teach affinity purification of antibodies.

The secreted form of the EPO receptor of D'Andrea includes at least 25 amino acids extending beyond the region of the erythropoietin receptor extracellular domain. At column 19, lines 54-56, D'Andrea states that the secreted form of the EPO receptor is encoded by nucleotide -70 to 845 of Fig. 9 and 9A. This renders the secreted form of the EPO receptor of D'Andrea significantly larger and of a different chemical structure than EPO-bp of the current application. Those additional amino acids contain a signaling peptide that carries a separate functionality and possibly additional extraneous sequence. The difference can be seen by comparing the secreted form of the EPO receptor of D'Andrea with a molecular weight of approximately 32 kilodaltons in contrast to the EPO-bp of the present invention with a molecular weight of 29 kilodaltons.

The expression of the peptide of D'Andrea as taught in Harris is not the equivalent of the EPO-bp of the present invention as suggested by the Examiner. The teaching of D'Andrea and Harris both produce polypeptides with extraneous sequence outside of the extracellular domain of human EPO receptor. The EPO-bp of the present invention is a purified peptide corresponding to only the extracellular domain of human EPO without the inclusion of extraneous domains. The current application further shows as part of Example 6 on page 25 of the Specification that further cleavage to a 20 kDa peptide, corresponding to approximately the removal of 30 additional amino acids from EPO-bp, causes a loss in activity that prevents recognition by EPO-bp specific antibodies. This demonstrates that addition or subtraction of even a few amino acids can result in unexpected changes in peptide function.

D'Andrea discloses the use, not the method for obtaining antibodies to the complete murine EPO receptor and human EPO. D'Andrea suggests the production of antibodies to complete EPO receptor but does not teach a method for affinity purification of those antibodies. D'Andrea does not suggest or teach the production of purified antibodies to a purified extracellular domain peptide as in the present invention. Although the Examiner asserts that D'Andrea teaches the use of the EPO receptor as an affinity reagent for the purification of EPO, there is no suggestion for the affinity purification of antibodies by an EPO receptor excellular domain or any other protein.

Harris does not overcome the inadequacies of D'Andrea. Although, Harris successfully uses a prokaryotic expression vector, the fusion protein achieved is not capable of cleavage with XA factor as proposed in disclosure of Harris. Neither Harris nor D'Andrea teach or suggest the production of antibodies to the EPO receptor extracellular domain. There are no teachings in either Harris or D'Andrea directed to the creation of affinity reagents carrying the inventive antibody. Consequently, Harris in view of D'Andrea does not render obvious the purified antibodies to EPO-bp of the present invention, the affinity agents using those antibodies nor the method for obtaining said antibodies using EPO-bp.

35 USC §112

The Examiner objected under 35 U.S.C. § 112 to the language "....capable of binding...." in claims 3 and 8 because the language was not supported by the specification for failure to teach modification to result in binding. Additionally, the language was objected to for not being a true limitation.

Claims 3 and 8 have been amended to alleviate the Examiner's objection to the language "capable of binding." The amended claims contain language describing the purified extra- cellular domain of the EPO receptor as having a binding affinity for EPO. The binding affinity of EPO-bp to EPO was demonstrated and characterized in the application by the binding experiments between the extracellular domain, EPO-bp and EPO carried out therein.

The Examiner objected under 35 U.S.C. § 112 to claims 3, 5, 6, and 9 as being indefinite for failing to particularly point out and distinctly claim the subject matter of the present invention.

Claim 3 has been amended to more clearly define the invention as being to the free human erythropoietin extracellular domain, thereby alleviating the Examiner's objection for being indefinite.

Claims 5, 6 and 9 are amended to make the language consistent with that found in the specification. Claims 5, 6, and 9 are not indefinite in view of the description provided in the specification. The terms "solid phase reagent" and "immunoassay composition" appear on page five of the specification. The solid phase reagent is further mentioned as having erythropoietin coupled thereto on page six. The descriptions on page five and six are part of the Summary of the Invention and therefore are a general overview of the specific aspects of the invention that are more specifically discussed in the Detailed Description of the Invention. Specific examples of solid phase reagents and immunoassay compositions are demonstrated in Examples five and six.

Claims 6 and 9 are directed to immunoassay compositions concerning the operable coupling of EPO-bp antibodies to a solid phase reagent. The description of a solid phase reagent and the antibody operably coupled to the solid phase reagent is supported by the

specification at pages 5-6 and in Examples 5 and 6 at pages 21-26. Example 5 describes the purification of antibodies using an EPO-bp affinity column. The antibodies which specifically bind to EPO-bp become operably coupled to the column material and remain coupled thereto until eluted. Example 6 demonstrates coupling of antibodies to a nitrocellulose membrane through binding action to EPO-bp. Both examples demonstrate operable coupling of antibodies to solid phase reagents as described in Claims 6 and 9.

Claim 5 is directed to the coupling of the EPO-bp peptide to a solid phase reagent. Example 6 on pages 24-26 of the specification describes washing Affi-gel® beads and incubating the EPO-bp peptide with the bead to allow binding and then washing the beads to remove unbound peptides. The Affi-gel® beads disclosed are one example of possible solid phase supports that may possibly be used in these types of assays. The beads may be used as shown in example six where they are simply mixed with the other proteins to be tested for binding. Example five discloses another use where an EPO-bp affinity column prepared from EPO-BP and Affi-gel® 15 agarose in the same manner as the EPO-bp Affi-gel® beads described in example six. In addition, it is known in the art that other solid phase supports may be used such as membrane filers, for example the nitrocellulose on page 23, gels, such as the SDS-PAGE gel on page 23 and beads or agarose of different sizes, shapes or materials, of which Affi-gel® 15 agarose is one example.

Applicant requests the reconsideration of claims 5, 6 and 9 under 35 U.S.C. § 112 in light of the above statements highlighting the relationship between the Summary of the Invention located of pages five and six of the specification to the experiments as performed in the Detailed Description of the Invention. Claims 5, 6, and 9 are not indefinite when considered in view of the full Specification.

With this amendment, the Examiner is asked to consider the earnest effort to address all issues raised in the Office Action of September 25, 2002. Applicants respectfully submit that the application is now in condition for allowance.

Respectfully submitted,

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APPENDIX:
MARKED UP VERSION OF SPECIFICATION AND CLAIM AMENDMENTS

3. (Four times amended) A [fusion protein consisting of an upstream portion, a cleavage site, and a human erythropoietin receptor] polypeptide consisting of a human erythropoietin receptor extracellular domain, said [human erythropoietin receptor] polypeptide [being capable of binding] having a specific affinity for human erythropoietin, wherein said [fusion protein is expressed at high levels, purified by affinity chromatography and cut at the cleavage site producing free human erythropoietin receptor extracellular domain] polypeptide has a molecular weight of 29 kDa and contains only amino acids corresponding to the extracellular domain of the human erythropoietin receptor.

4. (Twice amended) A purified antibody having specific binding affinity for human erythropoietin receptor, said antibody produced against a purified fragment of human erythropoietin receptor extracellular domain with a molecular weight of 29 kDa, wherein the fragment contains only amino acids corresponding to the extracellular domain of the human erythropoietin receptor.

5. (Amended) An [immunoassay] binding assay composition comprising:
(a) a solid phase [immunoassay] reagent; and
(b) the [protein] polypeptide of claim 3 operably coupled to said reagent.

6. (Amended) An immunoassay composition comprising:
(a) a solid phase [immunoassay] reagent; and
(b) an antibody of claim 4 operably coupled to said reagent.

8. (Twice amended) A purified antibody having specific binding affinity for a purified human erythropoietin receptor extracellular domain polypeptide, wherein said polypeptide is expressed in E-coli, [capable of binding] has an affinity for human erythropoietin, and does not include any amino acids from non-human DNA.

9. (Amended) An immunoassay composition comprising:
(a) a solid phase [immunoassay] reagent; and
(b) an antibody of claim 8 operably coupled to said reagent.

10. (Amended) A method for obtaining an antibody having specific binding affinity for human erythropoietin receptor polypeptide, said method comprising:
contacting a non-human mammal with a purified preparation of an extracellular domain fragment of human erythropoietin receptor polypeptide, wherein the fragment contains only native human erythropoietin receptor and has a molecular weight of 29 kDa, and
collecting said antibody from said non-human mammal.